Developmental Immunotoxicity: A Proposed Testing Framework

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Concerns have been raised regarding the adequacy of assessment for potential effects on the developing immune system in human health risk assessment. In order to reach consensus regarding the most appropriate methods to assess developmental immunotoxicity (DIT) for hazard identification, a group of 30 immunotoxicology experts from the United States and the European Union, representing government (U.S. Environmental Protection Agency [U.S. EPA], Food and Drug Administration [FDA], National Institute of Occupational Safety and Health [NIOSH]), industry, and academia, was assembled by the ILSI/HESI Immunotoxicology Technical Committee (ITC). In a roundtable discussion format, the participants addressed the following points:

• Current regulatory expectations for DIT testing guidelines
• Potential triggers that would cause regulatory agencies to require a DIT test
• The extent to which DIT testing can be incorporated into other test protocols
• The role of pathology in assessing DIT
• The most appropriate study design (species and strain, age at assessment, route of administration, ensuring adequacy of exposure)
• The most appropriate immune assays or endpoints
• Additional research needed.

The major conclusions of the roundtable discussions (Holsapple et al., 2005) were that (1) the rat is the preferred model for testing; (2) any DIT protocol should be based upon immune assays that are already validated; (3) to the extent possible, DIT assays should be incorporated into standard developmental and reproductive toxicity tests; (4) the approach to DIT testing should be similar for environmental toxicants and pharmaceuticals, although flexibility should be used in designing studies in order to address specific questions; (5) a study design can be used that assesses all critical windows of immune system development in one test, and additional follow-up testing can be conducted if deemed appropriate; (6) animals should be exposed throughout the treatment period; and (7) the triggers for DIT testing can include structure–activity relationships, results from other toxicity studies, the intended use of a chemical/pharmaceutical, and/or its

anticipated exposure of neonates and/or juveniles. The results of this roundtable discussion will be useful in U.S. EPA efforts to develop and validate a DIT test guideline.

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